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**Traumatic brain injury: a risk factor for neurodegenerative diseases**

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**Abstract:** Traumatic brain injury (TBI), a major global health and socioeconomic problem, is now established as a chronic disease process with a broad spectrum of pathophysiological symptoms followed by long-term disabilities. It triggers multiple and multidirectional biochemical events that lead to neurodegeneration and cognitive impairment. Recent studies have presented strong evidence that patients with TBI history have a tendency to develop proteinopathy, which is the pathophysiological feature of neurodegenerative disorders such as Alzheimer disease (AD), chronic traumatic encephalopathy (CTE), and amyotrophic lateral sclerosis (ALS). This review mainly focuses on mechanisms related to AD, CTE, and ALS that are induced after TBI and their relevance to the advancement of these neurodegenerative diseases. This review encompasses acute effects and chronic neurodegenerative consequences after TBI for a better understanding of TBI-induced neuronal death and to design therapies that will effectively treat patients in the primary or secondary progressive stages.

**Keywords:** Alzheimer disease; amyotrophic lateral sclerosis; chronic traumatic encephalopathy; neurodegeneration; traumatic brain injury.

**Introduction**

Global deaths from injury increased by 10.7%, from 4.3 million deaths in 1990 to 4.8 million in 2013 (Naghavi et al., 2015). Injuries accounted for 9% of the world’s deaths in 2000 and 12% of the world’s burden of disease and will surpass many diseases as a major cause of death and disability by the year 2020 (Hyder et al., 2007).

**TBI: a chronic disease process**

Brain injury leads to tissue deformation at the time of injury, damages blood vessels, shears axons, and produces cellular damage (Prins et al., 2013). TBI initiates a process that induces molecular, biochemical, and cellular changes, which in turn contribute to ongoing neuronal damage and death over time. This continuing damage is known as secondary injury and triggered multiple and multidirectional events, including, but not limited to, excitotoxicity...
R. Gupta and N. Sen: Traumatic brain injury augments proteinopathy oxidative stress, apoptosis, inflammation edema, cerebral metabolic, and mitochondrial dysfunction (MacFarlane and Glenn, 2015), as shown in Figure 1. These secondary events presented after TBI leads to the other, and the result is greater damage than the initial insult (Gupta and Kanungo, 2013; Gupta and Prasad, 2014, 2015).

Secondary mechanisms associated with TBI

The initial surge of glutamate at the time of injury leads to excitotoxicity that involves the activation of complex biochemical and cellular pathways that produce prolonged depolarization of neurons by activating N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, leading to the influx of calcium and other ions into the cell (Luo et al., 2011; Gupta and Prasad, 2013). Swelling occurs because of the osmotic shift of water, and strident sodium ion influx depolarizes the neuronal membrane, which leads to the development of cytotoxic edema. Aquaporin 4 (AQP4) is known to predominantly contribute to cytotoxic edema. TBI stimulates nuclear translocation of several transcriptional factors, including Foxo3a in astrocytes, and subsequently augments their binding to AQP4 promoter in pericontusional cortex. The nuclear accumulation of Foxo3a is augmented by a decrease in phosphorylation at its Ser256 residue because of the inactivation of Akt after TBI. The depletion of Foxo3a in mice rescues cytotoxic edema by preventing the induction of AQP4 and attenuates memory impairment after TBI in mice (Kapoor et al., 2013).

The increased calcium influx leads to the activation of several cellular pathways, including the calcium-dependent enzymes nitric oxide synthases (NOS) and phospholipases, which cause the production of free nitrogen radicals and reactive oxygen species (ROS); this leads to further excitotoxic damage (Xiong et al., 2001). The mechanisms of secondary injury after TBI also include an inflammatory response. The immediate response of the brain to an insult is characterized by the activation of microglia in the brain parenchyma (Hinson et al., 2015), accompanied by the infiltration of activated leucocytes from the periphery (Lee et al., 2014) through a disrupted blood-brain barrier (BBB) or transendothelial migration and diapedesis. The inflammatory response in the brain after TBI is dependent on the increased release of proinflammatory cytokines tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), and IL-6 and an increased expression of adhesion molecules such as intercellular adhesion molecule-1 (Hang et al., 2005). Further, ROS are highly reactive molecules implicated in the pathology of TBI through a mechanism known as oxidative stress (Rodriguez-Rodriguez et al., 2014). There are two main families of free radicals: ROS and reactive nitrogen species. The production of O2- is a consequence of normal metabolism, and this species is a precursor to hydrogen peroxide (H2O2), which can generate hydroxyl radicals (-OH) via the Fenton reaction. The -OH is one of the most reactive chemical species. The reaction of O2- with nitric oxide (NO·) produces peroxynitrite (ONOO-). After brain injury, the levels of ROS production overwhelm scavenging systems and result in oxidative damage (Slemmer et al., 2008). Moreover, TBI-induced intracellular Ca2+ accumulation can activate numerous enzymes, including xanthine dehydrogenase, phospholipase A2, and NOS, which increase O2- and NO· production (Shohami et al., 1997), which can cause widespread oxidative damage because of their ability to induce pathological changes in lipids, proteins, DNA, membrane structures, and mitochondria (Massaad and Klann, 2011). The ROS-induced lipid peroxidation of the cell membranes results in membrane disintegration and increased microvascular permeability (Cristofori et al., 2001).

In addition, ROS can promote inner mitochondrial membrane permeability that forces the rupture of the outer membrane and the release of cytochrome c through the mitochondrial permeability transition. The intracellular cytochrome c then causes the formation of the ‘apoptosome complex’ (Apaf1, dATP, and caspase-9), which in turn activates a family of cysteine proteases known as caspases3 (Cheng et al., 2012). Caspases play a crucial role in mediating apoptosis, probably by cleaving multiple cellular proteins ultimately causing cell death. Alternatively,
a caspase-activating complex is initiated by the binding of ‘death factors’ such as Fas ligand to cell surface receptors belonging to the TNF/nerve growth factor receptor superfamily (Qiu et al., 2002). Akt, a well-known prosurvival protein, promotes survival and growth in response to activation by extracellular signals. However, TBI induces the expression of GADD34 by stimulating the binding of a stress-inducible transcription factor, ATF4, to the GADD34 promoter. GADD34 then binds with TRAF6 and prevents its interaction with Akt. This event leads to the retention of Akt in the cytosol and prevents phosphorylation at the T308 position and, thus, ceases Akt activation (Farook et al., 2013). However, neuronal death is heterogeneous and exhibits morphological characteristics that may represent a continuum between necrosis and apoptosis (Elmore, 2007). It is now clear that after TBI, both apoptosis and necrosis are observed, affecting astrocytes and oligodendroglial cells as well as neurons (Raghupathi, 2004). However, detailed mechanism about molecular responses after TBI is far from clear, and more research for step-by-step proceedings after TBI may help to develop future interventions to reduce secondary injury.

**TBI: a risk factor for neurodegenerative diseases**

Research from past decade has drawn much attention of the long-term pathological consequences of TBI. The varying degree of injury is associated with the progressive atrophy of gray and white matter structures that may persist months to years after injury. In addition, several reports link single or repetitive injury with AD, CTE, and ALS, which results in the gradual degeneration of brain cells and gradual loss of brain functions.

**TBI and AD**

AD is a progressive, neurodegenerative disease characterized by deteriorating cognitive abilities, dementia, and memory loss (Bettcher and Kramer, 2014). Cognitive deficits that can follow TBI include impaired attention; disrupted insight, judgment, and thought; reduced processing speed; distractibility; and deficits in executive functions such as abstract reasoning, planning, problem solving, and multitasking (Tsaousides and Gordon, 2009). Memory loss, the most common and devastating cognitive impairment among TBI patients, occurs in 20%–79% of people with closed head injury, depending on severity (Hall et al., 2005). Evidences from humans (DeKosky et al., 2007) and experimental animal models (Yoshiyama et al., 2005) have revealed abnormal accumulations of extracellular senile plaques and intracellular neurofibrillary tangles (NFTs).

**Underlying mechanisms for TBI-induced formation of NFTs and Aβ plaques**

Senile plaques are formed of aggregates of amyloid beta (Aβ) peptides, whereas NFTs are composed of bundles of paired helical filaments, which are made up of aberrantly phosphorylated tau microtubule-associated proteins. A recent study has shown that long-term survivors of just a single moderate-to-severe TBI exhibited abundant and widely distributed NFTs and Aβ plaques in approximately one-third of the cases, but this was exceptionally rare in uninjured controls (Johnson et al., 2012). Surprisingly, the plaques found in TBI patients are strikingly similar to those observed in the early stages of AD (Ikonomovic et al., 2004). Such findings demonstrate the long-term consequences of a single TBI event (Jordan, 2014).

Moreover, secondary neuronal injury in chronic neurodegenerative diseases or acute brain injury is mainly mediated by neuroinflammatory responses (Chen et al., 2014). The early phase of microglial activation in response to brain injury is accompanied by increased levels of IL-10 and TGF-β, which are generally regarded as anti-inflammatory cytokines that are capable of mediating neural protection and regeneration. Anti-inflammatory microglia with phagocytic properties have the potential to clear Aβ species and β-amyloid plaques; remarkably, Aβ-containing microglia have been found in association with plaques after TBI (Breunig et al., 2013). Glial activation results in the upregulation of APP as well as other inflammatory mediators that contribute to a cycle of Aβ deposition and microglial activation, which ultimately result in chronic neuropathology. Postcontusion axonal injury and impaired axonal transport are being speculated as a trigger that initiates a disease process and responsible for long-term symptoms (Johnson et al., 2013).

Axonal swelling observed after TBI has been ascribed to cytoskeletal alteration and interruption of protein transport (Tang-Schomer et al., 2012). TBI also induces α-synuclein, APP, BACE1, tau, ApoE4, PS1, and caspase-3, which in turn may involve in APP processing contributing to AD (Breunig et al., 2013). Moreover, studies in various animal models indicate that the expression of amyloidogenic β- and γ-secretases and their substrate APP is increased after TBI, suggesting that Aβ peptides...
are generated de novo after TBI (Chow et al., 2010; Haass et al., 2012). Interestingly, recent studies have shown that the intracerebral infusion of brain extracts containing aggregated Aβ can initiate Aβ deposition in brains of APP transgenic mice (Bolmont et al., 2007; Rosen et al., 2012). In addition, these Aβ peptides can spread from the site of injection to other brain regions as these Aβ accumulations can migrate between axonally interconnected areas (Jucker and Walker, 2011). Thus, amyloid pathology, spreading from the site of the TBI to other areas, potentially suggests a mechanism for the secondary injury to the areas that were not directly subjected to the TBI but show AD-type pathological lesions.

After TBI, hypoxia and hypertension are common (Frugier et al., 2010; Huang et al., 2010). Hypoxia facilitates the pathogenesis of AD by accelerating the accumulation of Aβ and by increasing the hyperphosphorylation of tau, leading to the chronic process of neurodegeneration (Zhang and Le, 2010). Hypoxia markedly increases Aβ deposition and potentiates memory deficits in AD (Sun et al., 2006). Accumulating evidences show that stroke and ischemic attacks significantly increase the risk of AD because of the drive in cerebral Aβ accumulation and related to apoptotic events in the brain (Wen et al., 2004; Tesco et al., 2007).

TBI also affects the ubiquitin-proteasome system as a significant reduction in the level of free ubiquitin protein is reported after TBI (Staal et al., 2009). In the ubiquitinproteasome pathway (UPP), abnormal proteins to be degraded are first conjugated by polyubiquitin chains and then degraded by proteasomes (Lecker et al., 2006). The UPP has been linked to several neurodegenerative diseases (Schwartz and Ciechanover, 1999). Recent reports suggest the link between the dysregulation of the ubiquitin-protease system and an accumulation of Aβ levels in TBI (Magnoni and Brody, 2010); however, our understanding about involvement of these processes is far from clear.

**TBI and CTE**

**Symptoms associated with CTE**

Also called dementia pugilistica, CTE primarily affects individuals with a history of repetitive closed head injury, most often occurring to career boxers (Corsellis, 1989). Although CTE is a manifestation of repetitive trauma, few reports suggest that single TBI is sufficient to induce CTE (Blaylock and Maroon, 2011). However, this theory needs more speculations to go strong. In general, CTE leads to cognitive, behavioral, and physical impairments and has recently been linked to other contact sports, including American football and ice hockey as well as military service (McKee and Robinson, 2014). The initial symptoms are typically insidious, consisting of irritability, impulsivity, aggression, depression, short-term memory loss, and heightened suicidality (Stein et al., 2014). The symptoms progress slowly over decades to include cognitive deficits and dementia.

**CTE contributes to tauopathy and neurological diseases associated with protein aggregation**

Repeated traumatic injury, even with mild impact, can damage axons and cause changes in membrane permeability and ionic shifts, leading to the large influx of calcium (Giza and Hovda, 2001). The subsequent release of caspases and calpains would trigger tau phosphorylation, misfolding, shortening, and aggregation as well as cytoskeleton failure with the dissolution of neurofilaments and microtubules. Head injury in the acute setting activates microglia that release toxic levels of cytokines, chemokines, immune mediators, and excitotoxins such as glutamate, aspartate, and quinolinic acid. These excitoxins inhibit phosphatases, which results in hyperphosphorylated tau and eventually neurotubule dysfunction and NFT deposition in particular areas of the brain (Saulle and Greenwald, 2012). Moreover, the pathology of CTE is characterized by the accumulation of phosphorylated tau protein in neurons and astrocytes. CTE is distinguished from other neurodegenerative disorders by a distinctive topographic and cellular pattern of tau neurofibrillary pathology. The hyperphosphorylated tau abnormalities begin focally as perivascular NFTs and neurites at the depths of the cerebral sulci and then spread to involve superficial layers of adjacent cortex before becoming a widespread degeneration affecting medial temporal lobe structures, diencephalon, and brainstem (McKee et al., 2009). CTE has been categorized into stages I–IV based on the increased severity of protein deposition, cerebral atrophy, and behavioral sequel (McKee et al., 2013), as shown in Table 1. Compared with AD, the size of individual NFTs in CTE is generally larger, and the neurites are less threadlike and more dotlike and spindle shaped. The tendency of the phosphorylated tau (p-tau) neurofibrillary pathology in CTE to be around BBB and irregularly concentrated at the sulcal depths was also noticed (Blaylock and Maroon, 2011).
Table 1: Neuropathological staging of chronic traumatic encephalopathy.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Topographical pattern of NFTs</th>
<th>Clinical symptoms</th>
<th>Macroscopic observation</th>
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<tr>
<td>I</td>
<td>Perivascular NFTs in focal epicenters at the depths of the sulci in the superior, superior lateral, or inferior frontal cortex</td>
<td>Headache and loss of attention and concentration</td>
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<tr>
<td>II</td>
<td>NFTs in superficial cortical layers adjacent to the focal epicenters and in the nucleus basalis of Meynert and locus coeruleus</td>
<td>Depression and mood swings, explosivity, loss of attention and concentration, headache, and short-term memory loss</td>
<td>Mild cerebral atrophy, septal abnormalities, ventricular dilatation, a sharply concave contour of the third ventricle, and depigmentation of the locus coeruleus and substantia nigra</td>
</tr>
<tr>
<td>III</td>
<td>Dense NFTs in medial temporal lobe structures (hippocampus, entorhinal cortex, and amygdala) and widespread regions of the frontal, septal, temporal, parietal and insular cortices, diencephalon, brainstem, and spinal cord</td>
<td>Cognitive impairment with memory loss, executive dysfunction, loss of attention and concentration, depression, explosivity, and visuospatial abnormalities</td>
<td>Cerebral, medial temporal lobe, hypothalamic, thalamic and mammillary body atrophy, septal abnormalities, ventricular dilatation, and pallor of the substantia nigra and locus coeruleus</td>
</tr>
<tr>
<td>IV</td>
<td>Dense NFTs involved widespread regions of the neuraxis, including white matter, with prominent neuronal loss and gliosis of the cerebral cortex and hippocampal sclerosis</td>
<td>Uniformly demented with profound short-term memory loss, executive dysfunction, attention and concentration loss, explosivity, and aggression. Most also showed paranoia, depression, impulsivity, and visuospatial abnormalities</td>
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β-Amyloid aggregates are only found in 40%-50% of CTE cases, are significantly associated with age at death, and are not a characteristic of early CTE. In CTE, β-amyloid is found predominantly as diffuse plaques in low densities (McKee et al., 2009). α-Synuclein-positive Lewy bodies are found in approximately 20% of CTE cases and are significantly associated with the age of the subject at death (Uryu et al., 2007). Further, McKee et al. (2010) have found widespread TAR DNA-binding protein (TDP-43) inclusions in 10 of 12 cases of CTE. In early stages, the inclusions consist of neuritic threads and dotlike inclusions typically found in subpial, perivascular, and periventricular regions. The TDP-43 inclusions in CTE partially colocalize with p-tau inclusions in neurons. TDP-43 binds to many cellular transcripts, including tau and α-synuclein, and its dysregulation may underlie some of the pathologies seen with these proteins (McKee et al., 2010). However, much research is needed to understand the role of TDP-43 in pathology of CTE.

TBI and ALS

ALS, often referred to as Lou Gehrig disease or Charcot disease, is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. ALS is the most common motor neuron disease affecting approximately 0.8–8.5 people per 100 000 worldwide (Roman, 1996). The disorder causes muscle weakness and atrophy throughout the body because of the degeneration of the upper and lower motor neurons. Individuals affected by the disorder may ultimately lose the ability to initiate and control all voluntary movement, although bladder and bowel function and the muscles responsible for eye movement are usually spared until the final stages of the disorder (Kiernan et al., 2011). Sensory nerves and the autonomic nervous system are generally unaffected, meaning the majority of people with ALS maintain hearing, sight, touch, smell, and taste. Cognitive function is generally spared for most people, although some (approximately 5%) may develop frontotemporal dementia (Achi and Rudnicki, 2012). A higher proportion of people (30%-50%) also have more subtle cognitive changes, which may be unnoticed but are revealed by detailed neuropsychological testing. ALS coexists in individuals who also experience dementia, degenerative muscle disorder, and degenerative bone disorder as part of a syndrome called multisystem proteinopathy.

Risk factors associated with TBI-induced ALS

Many risk factors have been considered as possible triggers of the neurodegenerative sequel in ALS, including a history of trauma to the brain and spinal cord (Chen et al., 2007). It is shown that initial lesions to the motor cortex may be a contributing initiating factor in some patients with ALS or determine the site of onset in individuals predisposed to ALS (Rosenbohm et al., 2014). Further, epidemiological research has identified an increased risk...
of ALS in individuals likely to suffer head trauma, such as football players, soccer players, and military veterans (Chio et al., 2005). Recent literature points toward a trend between brain trauma and ALS development. Case studies of patients suffering traumatic axonopathy to the lower motor neurons are vulnerable to later developed ALS (Riggs, 1985). Riggs has proposed several hypothetical mechanisms that could explain traumatic axonopathy, increasing the risk of ALS. Recently, it was shown that some professional athletes (football and boxing) who have had repeated head injuries and developed what is called CTE may develop ALS (McKee et al., 2010). This study, based on the examination of the brain and spinal cord at autopsy, indicated that some pathological features of CTE in the brain can extend to the spinal cord. The author suggested that traumatic axonal injury may induce caspase death cascade, impaired axonal transport, impairment of retrograde transport, and separation of the axon from its target (Riggs, 1993). Further, lower motor neurons in ALS show axonal swelling and protein aggregates relatively early in disease progression.

The accumulation of neurofilaments and the disruption of retrograde transport may suggest a potential mechanism initiating ALS. Moreover, it is estimated that 90%–95% of ALS cases are sporadic, and gene mutations in copper/zinc superoxide dismutase 1, senataxin, and dynactin account for some familial forms of the disease (Shi et al., 2010). In addition, motor neurons in sporadic ALS often have ubiquitin- and TDP-43-immunoreactive inclusion bodies that appear either as rounded hyaline inclusions or as skein like inclusions (Leigh et al., 1991; Nonaka et al., 2009). It was also suggested that people with a genetic predisposition to neurotrophin deficiency may show increased vulnerability of motor neurons after trauma and consequently increased risk of ALS (Riggs, 1995).

Future prospectives

Many studies support the hypothesis that the survivors of TBI have a major risk of developing neurodegenerative diseases; however, it is a complex issue and requires extensive investigation for a better understanding. Axonal damage and impaired axonal transport due to TBI can induce both rapid and long-term accumulation of several key axonal proteins, including APP, α-synuclein, p-tau, TDP-43, and related peptides that normally do not encounter such high concentration in axons. This serves as a platform for increased processing and accumulation of Aβ plaques, NFTs, or other bodies/inclusions in brain. Persistent accumulation of such malfunctioning peptides in axons due to impaired transport after TBI suggests a continuing pathological process. In addition, very little is known about what type, frequency, or amount of trauma is necessary to induce the accumulation of these pathological proteins. Moreover, there is clearly a need for improved accuracy of clinical diagnostic criteria in the differential diagnosis of TBI-induced neurodegenerative diseases, which need new prospective longitudinal studies on specific biomarkers and also well-standardized criteria to diagnose them neuropathologically. Studies in both experimental models and human TBI patients will be required to identify the key components of the molecular cascades mechanism underlying the observed pathological protein dynamics and elucidate the reasons why TBI increases the risk of neurodegeneration (Johnson et al., 2012).

References


